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[Ru^{IV}(F₂₀-TPP)Cl₂] efficiently catalysed inter- and intra-molecular nitrene insertion into sp³ C–H bonds of hydrocarbons using phosphoryl azides as nitrene sources[†]

Wenbo Xiao,^a Jinhu Wei,^a Cong-Ying Zhou*^{ab} and Chi-Ming Che*^{ab}

 $[Ru^{IV}(F_{20}\text{-}TPP)Cl_2][H_2(F_{20}\text{-}TPP) = meso-tetrakis(pentafluorophenyl)$ porphyrin] is an active catalyst for both inter- and intra-molecularnitrene insertion into sp³ C–H bonds of hydrocarbons in good tohigh product yields using phosphoryl azides as nitrene sources.

The construction of C-N bonds is of paramount importance in organic synthesis due to the prevalence of amino groups in biologically active natural products and pharmaceuticals. Transition metal catalysed nitrene insertion into saturated C-H bonds is an appealing strategy for C-N bond formation.¹ Using this approach, the robust sp³ C-H bonds could be used as functionality for the construction of C-N bonds thereby obviating multi-step group transformations and allowing installation of nitrogen functionality in a selective manner. While iminoiodanes such as PhI = NTs and their in situ variants are the most commonly used nitrene sources for C-H amination, the generation of PhI as a byproduct renders the reaction less eco-friendly. Recently, the use of organic azides in nitrene transfer and insertion reactions has received a surge of interest as only nitrogen gas is produced as a byproduct. In addition, the stability and diversity of organic azides also render them promising nitrene sources for C-N bond forming reactions. Dirhodium(II) carboxylates,² ruthenium(II)³ and iridium(III)⁴ Schiff base complexes, copper β -diketiminates,⁵ and the porphyrin complexes of ruthenium(π),⁶ iron(π)⁷ and cobalt(π),⁸ all have been demonstrated to be effective catalysts for nitrene insertion into sp³ C-H bonds using organic azides. We recently reported that dichlororuthenium(IV) porphyrins such as [Ru^{IV}(TTP)Cl₂] (H₂TTP = meso-tetrakis(4-tolyl)porphyrin) are effective catalysts for nitrene insertion into aldehyde C-H bonds to give N-acylphosphoramidates in good to high yields using phosphoryl azides as nitrene sources.⁹ These findings prompted us to examine the feasibility of using $[Ru^{IV}(por)Cl_2][H_2Por = porphyrin]$ as catalyst for amination of saturated alkanes.

The [Ru^{IV}(Por)Cl₂] complexes (Fig. 1) were prepared by methods provided in the literature.^{10,11} [Ru(F₂₀-TPP)Cl₂] was prepared by the reaction of [Ru(F₂₀-TPP)O₂] with HCl.¹¹ It was characterized using ESI-MS (peaks at 1144.0 and 1109.0 attributed to [Ru(F₂₀-TPP)Cl₂]⁺ and $[Ru(F_{20}\text{-}TPP)Cl]^+$, UV-visible absorption spectroscopy ($\lambda_{max}(\log \varepsilon)$): 406 nm (5.01), 507 nm (3.91)), ¹H NMR (pyrrolic protons (H_{β}) at $\delta = -51.9$ ppm) and ¹⁹F NMR (three sets of peaks at $\delta = -129.7$, -148.9, -158.9 ppm). In our preliminary study, we examined the reactivities of a panel of stabilized organic azides including phosphoryl azides, sulfonyl azides and acyl azides used in limiting amounts towards C-H amination of cyclohexanes used in excess with [Ru^{IV}(TDCPP)Cl₂] as catalyst (Table 1). Treatment of cyclohexane (20 equiv.) with 4-nitrobenzenesulfonyl azide 2a (1 equiv.) in the presence of [Ru^{IV}(TDCPP)Cl₂] (2 mol%) in 1,2-dichloroethane under reflux (84 °C) for 12 h afforded the amination product 3a in 25% yield based on 60% substrate (4-nitrobenzenesulfonyl azide 2a) conversion (Table 1, entry 1). When 2,2,2-trichloroethyl sulfazidate 2b was used, the corresponding amination product was obtained in 40% isolated yield (entry 2). Compared to 2a and 2b, 2,2,2-trichloroethoxycarbonyl azide 2c was more effective giving the amination product 3c in 90% yield and with 70% substrate conversion (entry 3). Phosphoryl azide 2d, which was previously reported to be effective for ruthenium porphyrin catalysed nitrene insertion into C-H bonds of aldehydes, failed to induce sp3 C-H amination of cyclohexane (entry 4). In contrast, phosphoryl azide 2e bearing the 2,2,2-trichloroethyl electron-withdrawing substituent



Fig. 1 Dichlororuthenium(IV) porphyrins.

^a Department of Chemistry and State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China.

E-mail: cmche@hku.hk, cyzhou@hku.hk; Fax: +85228571586; Tel: +85228592154

^b HKU Shenzhen Institute of Research & Innovation, Shenzhen, China

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Table 1 $[{\rm Ru}^{\rm IV}({\rm TDCPP}){\rm Cl}_2]\text{-catalysed C–H amination of cyclohexane with stabilized organic azides^a$



^a Organic azide (0.1 mmol), cyclohexane (2 mmol, 20 equiv.), [Ru(TDCPP)Cl₂] (2 mol%), 4 Å MS (50 mg), DCE (1.5 mL), argon, reflux (84 °C) for 12 h. ^b Determined using ¹H NMR based on organic azide.
^c Based on substrate conversion.

displayed the best performance affording product **3e** in 83% yield and with 95% substrate conversion (entry 5).

Having established bis(2,2,2-trichloroethyl) phosphorazidate 2e as a suitable nitrene source for the amination of cyclohexane, we turned to examine the catalytic activity of other transition metal complexes for the reaction depicted in Table 2. While $[Ru^{IV}(TTP)Cl_2]$ and $[Ru^{IV}(p\text{-}CITPP)Cl_2]$ displayed modest catalytic activity (Table 2, entries 1 and 2), $[Ru^{IV}(F_{20}\text{-}TPP)Cl_2]$ was found to efficiently catalyse amination of cyclohexane in 93% product yield and with 100% conversion of phosphoryl azide 2e (entry 3). The ruthenium(II) porphyrins $[Ru^{II}(TDCPP)(CO)]$ and $[Ru^{II}(F_{20}\text{-}TPP)(CO)]$ were less effective than their Ru(IV) counterparts giving 3e in low yields (entries 4 and 5). The iron(III) porphyrins ([Fe(TTP)CI]] and $[Fe(F_{20}\text{-}TPP)CI]$) and dirhodium(II) carboxylates $(Rh_2(OAC)_4 \text{ and } Rh_2(esp)_2^{-12})$ all failed

Table 2 Screening of catalysts for C–H amination of cyclohexane with phosphoryl azide $2e^{\rm a}$

	+ N ₃ -P(OCH ₂ CCl ₃) ₂ Catalys 2e Argon,	t (2 mol%) IS,DCE reflux 12h	0 H II N−P(OCH₂CCI₃)₂ 3e
Entry	Catalyst	Conv. ^{b} (%)	Yield ^c (%)
1	[Ru ^{IV} (TTP)Cl ₂]	42	40
2	$[Ru^{IV}(p-C TPP)Cl_2]$	77	41
3	Ru ^{IV} (F ₂₀ -TPP)Cl ₂	100	93
4	[Ru ^{II} (TDCPP)(CO)]	94	39
5	[Ru ^{II} (F ₂₀ -TPP)(CO)]	47	57
6	[Fe(TTP)Cl]	NR^d	
7	[Fe(F ₂₀ -TPP)Cl]	NR	
8	$[Rh_2(OAc)_4]$	NR	
9	[Rh ₂ (esp) ₂]	NR	

 a **2e** (0.1 mmol), cyclohexane (2 mmol, 20 equiv.), catalyst (2 mol%), 4 Å MS (50 mg), DCE (1.5 mL), argon, reflux (84 °C) for 12 h. ^{*b*} Conversion was determined based on **2e** using ¹H NMR and ³¹P NMR. ^{*c*} Based on substrate conversion. ^{*d*} NR = no reaction.

to catalyse this reaction under the same conditions (entries 6–9). No reaction was observed in the absence of a metal catalyst.

With the optimized reaction conditions, the substrate scope of [Ru^{IV}(F₂₀-TPP)Cl₂]-catalysed nitrene insertion into sp³ C-H bonds of hydrocarbons with 2e was examined. As depicted in Table 3, a variety of hydrocarbons including aliphatic and benzylic ones underwent C-H amination in good to high product yields. For example, cyclopentane and cyclooctane displayed similar activity to cyclohexane giving the corresponding aminated products in 81% and 86% yields respectively (entries 1 and 2). The reaction of ethylbenzene with 2e afforded benzylic C-H amination product 3h in 81% yield (entry 3). Likewise, when tetralin and indane were subjected to the Ru(w)catalysed amination, the benzylic C-H amination products 3i and 3k were obtained in 81% and 85% yields, respectively (entries 5 and 6). The use of sterically hindered diphenylmethane as a substrate led to slightly lower product yield (64%, entry 7). It is worth noting that the benzylic 1° C-H bonds of toluene compounds could be aminated in 62-85% yields (entries 8-10). When cyclohexene was used, allylic C-H amination product 3p was obtained in 76% yield without aziridination detected (entry 11). The reactivity of acyclic alkanes towards the Ru(IV)-catalysed C-H amination has also been examined. The reaction of hexane with 2e afforded a mixture of regioisomeric aminated products in an overall 76% yield with low regioselectivity (entry 12). When the branched alkane 2,3-dimethylbutane was employed as the substrate, only a trace amount of amination product was detected using ³¹P NMR and ¹H NMR, revealing a predominant steric effect of phosphoryl azides on the nitrene C-H insertion since a 3° C-H bond should be the site of attack as it has been reported to be more reactive than the 1° and 2° ones in C-H amination reactions with sulfonylamides and carbamates as nitrene sources.1

The intramolecular version of this Ru(Iv)-catalysed nitrene insertion into sp³ C–H bonds has been examined. Treatment of **4a** with [Ru^{IV}(F₂₀-TPP)Cl₂] (2 mol%) in dichloroethane under reflux for 12 h afforded benzylic C–H amination product **5a** in 99% yield (Scheme 1, eqn (1)). Likewise, when **4b** was used, nitrene insertion into aliphatic C–H bonds giving **5b** in 80% yield was observed. In these two examples, no five-membered cyclic product was observed. However, when the phosphoryl azide **4c** lacking the 2° C–H bond at the γ position was subjected to this Ru(IV)-catalysis, a five-membered amination product **5c** was selectively formed in 96% yield *via* nitrene insertion into the 3° C–H bond at the β position (Scheme 1, eqn (2)); the 1° C–H amination at the γ position was not observed. This result is in line with the order of reactivity of 3° > 2° > 1° C–H bonds. Similarly, **5d** was obtained in 91% yield *via* nitrene insertion into benzylic C–H bonds.

To gain insight into the reaction mechanism, the reaction of a mixture of cyclohexane and cyclohexane- d_{12} with N₃P(O)(OCH₂CCl₃)₂ (**2e**) was performed under the employed reaction conditions. A k_H/k_D value of 5.1 was obtained revealing that C–H bond cleavage is the rate determining step. This KIE value is in the range of 4.8–11 observed in stoichiometric C–H amination reactions of ethylbenzene and cyclohexene by bis(imido)ruthenium(vi) porphyrins, in which cases a H-atom abstraction mechanism has been suggested.¹³

In conclusion, an efficient intermolecular nitrene insertion into sp³ C-H bonds of hydrocarbons using phosphoryl azides has been developed. With $[Ru^{IV}(F_{20}\text{-}TPP)Cl_2]$ as catalyst and

Table 3 $[Ru^{IV}(F_{20}\text{-}TPP)Cl_2]$ -catalysed C–H amination of hydrocarbons with phosphoryl azide $2e^a$



^{*a*} **2e** (0.2 mmol), hydrocarbon (4 mmol, 20 equiv.), $[Ru(F_{20}\text{-TPP})Cl_2]$ (2 mol%), 4 Å MS (100 mg), DCE (3 mL), argon, reflux (84 °C) for 12 h. ^{*b*} Isolated yield. ^{*c*} **3q**: **3s** = 2.3 : 1 determined using ¹H NMR.

bis(2,2,2-trichloroethyl) phosphorazidate **2e** as a nitrene source, sp³ C-H bonds of hydrocarbons can be efficiently aminated in good to



high yields. Intramolecular nitrene C-H insertion has also been achieved in high product yields with $[Ru^{IV}(F_{20}-TPP)Cl_2]$ as catalyst.

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